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THE 1957 PANDEMIC OF INFLUENZA IN INDIA

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SYNOPSIS

Asian influenza appears to have reached India via Madras in May 1957. The main pandemic wave swept through the subcontinent within the next 12 weeks; cases occurring thereafter represent the permanent infiltration of the new virus into the population. Between 19 May 1957 and 8 February 1958 there were reported 4 451 758 cases, with 1098 deaths. The author discusses the attack-rates by age-group, by occupational group, by State and in closed communities such as schools. The disease, in India as elsewhere, seems generally to have run a mild course, although nausea and vomiting and symptoms related to the nervous system were relatively frequently seen.

A number of A/Asia/57 virus strains were isolated; their antigenic and biological characteristics are discussed in some detail. In view of the rapid spread of the pandemic, it proved impossible to prepare sufficient vaccine from the new strains in time for adequate field trials or mass immunization of the population.

The author reports briefly on the results obtained with iodine in the prevention and treatment of influenza.

Spread of the Pandemic

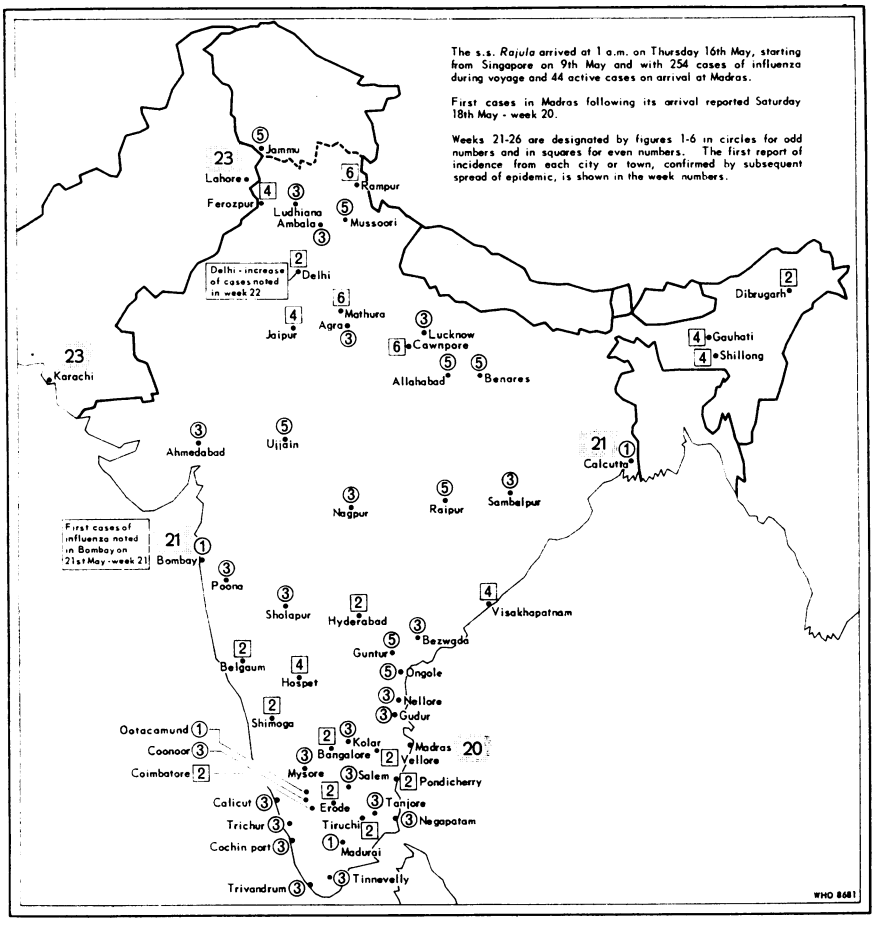
The first intimation that the influenza outbreak in South-East Asian countries such as Japan and Malaya was about to spread to India was received at the Government of India Influenza Centre at Coonoor on 11 May 1957. It was decided to keep a special watch on the arrival of infected cases at Calcutta and Madras and to isolate the virus from such cases. Information was received on 15 May that the s.s. *Rajula*, which had left Singapore on 9 May with 1622 passengers and about 200 crew members, had been directed to proceed to Madras instead of to its first port of call in India, Negapatam, in view of an outbreak of influenza on board affecting 254 persons in seven days. On the ship's arrival at Madras on the morning of 16 May it was found that there were 44 active cases of influenza on board, four of them showing temperatures above 103°F (39.4°C). The steamer was placed in quarantine at sea and was boarded by a medical

team which examined all on board and gave the necessary treatment. A laboratory team from Coonoor collected throat washings from the patients. These specimens were collected on 16 and 17 May and sent to Coonoor with adequate safeguards for preservation and safety in transit. In the laboratory at Coonoor, eggs were inoculated amniotically and the first isolation of the virus from the cases from the steamer was made on 22 May. The strain was sent to the World Influenza Centre in London and identified there as A/Asia/57 virus.

Four of the nurses who boarded the steamer on 16 May came down with fever on 18 May, i.e., 48 hours after exposure to infection. If this is taken as the first date of the epidemic in India, it can be stated that the pandemic was noticed in North China in January, Shanghai in February, Canton in March, Hong Kong in April, Singapore early in May and Madras in mid-May, or the 20th week of the year. The first cases in Bombay were reported on 21 May or in week 21, while Calcutta reported a few cases in the same week and over 1000 cases in week 22 with the first two deaths on 1 June. Whether the ports of Madras, Bombay and Calcutta were affected independently of each other or whether Madras was the first port to be affected and Bombay and Calcutta received infected cases from that city cannot be decided easily on the information available; the likelihood is that they were seeded independently but within a few days of each other by infected cases arriving by ship or aircraft. The southern States of Madras, Mysore, Kerala and Andhra appear to have received massive infection through the hundreds of passengers coming from Singapore by the two steamers s.s. *Rajula*, which discharged 1622 passengers on 21 May, and s.s. *State of Madras*, which discharged about 1065 passengers on 28 May. Medical examination of those on board the latter steamer on arrival at Madras revealed 49 active cases, besides 35 persons convalescing after attacks during the voyage. Another factor tending to confuse the issue was the report that there were several cases of influenza in the city of Madras before 15 May. It was not clear at that time whether they represented stray infections with the Asian virus or were due to type A or B virus strains current earlier in the country.

The spread of the epidemic through the Indian subcontinent, with particular reference to the chronological appearance of cases in different geographical areas, is shown in the map, which does not show, however, the intensity and duration of the outbreaks. The figures given against each town or city represent the week in the year when the first cases of influenza were reported from the area, 20 being the week when Madras was affected and 21 Bombay and Calcutta. For the sake of clarity, single numbers 1 to 6 are given against other areas, indicating weeks 21 to 26. The map is intended to show the speed with which the epidemic spread; within six weeks from 18 May it had spread all over India. In each area, the pattern was one of sweeping spread through the most crowded capital

WEEKLY SPREAD OF ASIAN INFLUENZA ON THE INDIAN SUBCONTINENT, 1957



and other cities, followed by a relatively slow spread across villages and other towns. Passengers from the s.s. *Rajula*, allowed to disembark on 21 May at Madras, arrived at Madurai and provided the starting-point of the outbreak in that city in week 21. The heavy influx of visitors from Madras city to Ootacamund for the annual flower show on 18 May was probably responsible for the sharp outbreak among the staff and students of the Lovedale School, commencing on 21 May and infecting 256 out of 533 children within five weeks. In the 22nd week, cases appeared for the first time in several widely separated areas, with a frequent history of arrival of infected persons or of contacts from infected towns. Thus 45 midwives returned from Madras to Coimbatore and six of them, along with eight nurses in contact with them, provided the first admissions of influenza to the Coim-

batore Hospital. In Thandaraiputhur Tiruchi District, a compounder returning from Madras developed influenza on 27 May and his contacts provided the next four cases. In Hyderabad, Andhra State, the primary focus was provided by a patient admitted to hospital on 26 May who had returned from Singapore in the s.s. *Rajula*. Bangalore and Mysore also each received one passenger from the s.s. *Rajula* on 27 May, and in the former city, three sick persons arriving by train from Madras on 31 May were removed to the infectious diseases hospital. Other towns and cities affected in the 22nd week were Erode and Vellore in Madras State, Belgaum and Shimoga in Mysore, Dibrugarh in Assam, and New Delhi, the capital. The source of infection is not clear in these areas.

It is worth while mentioning at this point that all three specimens of paired sera received from Assam from areas adjacent to Dibrugarh proved to be from patients suffering from type B influenza infections. Similar findings were made with sera from other towns such as Madras city and Madurai, where both Asian and type B infections were found, and Coimbatore, Tuticorin and Kozhikode, from which the particular specimens of sera sent all proved to be from type B cases. These findings explain the reported incidence of influenza in the city of Madras before the arrival of the infected steamer. It would thus appear that in 1957 type B virus was already causing several localized outbreaks in the country when the Asian virus arrived on the scene, and subsequently both of them spread in the population. There were several reports of patients having two attacks of influenza within two or three months. These were discounted at first, but the serological evidence obtained later of type B infection in the country lends support to them. The possibility that Assam may have received infection through Burma was considered, but, according to newspaper reports, Burma was still not affected as late as 5 June.

The maximum spread of the epidemic appeared to take place in the 23rd week (2-8 June). Over 60 passengers from the s.s. *Rajula* had arrived in various parts of the Palghat district of Kerala State and on 4 June, 12 persons in four families were down with influenza. Cochin port received its earliest cases by the s.s. *Indian Shipper* in this week, and had its first fatal case in the next week in a 60-year-old member of the crew of the s.s. *City of Chelmsford*. Trivandrum, the capital of the State, Trichur, Kozhikode and most of the bigger towns were severely affected in the 23rd week. In the same period, Mysore city and Kolar in Mysore State; Bezwada, Nellore, Gudur and other towns in Andhra; Poona, Nagpur, Ahmedabad and Sholapur in Bombay; Raipur and Sambalpur in Orissa; Lucknow and Agra in Uttar Pradesh; and Ludhiana and Ambala in the Punjab were among the numerous towns affected all over India. In the same week, Karachi, in Pakistan, had its earliest imported cases in a mother and child coming from Bombay by the s.s. *Dwaraka* on 3 June, and recorded 50 cases by the end of the week, 33 of them on 8 June. Lahore recorded 16 cases

TABLE 1. CUMULATIVE FIGURES FOR INFLUENZA CASES AND DEATHS IN INDIA FROM 6 JULY 1957 TO 8 FEBRUARY 1958 *

State	Total to 6 July 1957		Total to 10 August 1957		Total to 5 October 1957		Total to 7 December 1957		Total to 8 February 1958	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Andhra Pradesh	104 970		165 676	19	166 828	19	220 138	28	220 138	28
Assam	60 731		174 496	7	184 948	7	190 724	7	191 058	7
Bihar	? 5 000		136 359	17	153 708	18	155 082	18	155 146	18
Bombay	290 134		1 146 741	255	1 301 429	292	1 309 184	301	1 323 975	315
Kerala	146 337		255 648	9	225 858	9	289 253	9	289 265	9
Mysore	217 769		394 594	59	415 429	70	416 275	70	416 986	70
Madras	284 943		521 254	63	521 615	63	583 107	75	583 107	75
Madhya Pradesh	8 873		211 893	9	228 068	13	228 278	13	245 471	13
Orissa	26 314		140 822	12	151 212	12	151 325	12	151 398	12
Punjab	25 071		94 541	8	107 459	9	120 637	9	121 360	9
Rajasthan	13 314		50 142	10	53 007	10	56 685	10	58 346	10
Uttar Pradesh	43 235		187 701	48	244 142	53	268 331	54	270 661	64
West Bengal	72 775	211	155 852	314	263 340	404	282 491	437	289 048	445
Jammu and Kashmir			562				2 627		2 627	
Andamann and Nicobar	18		467		601	1	674	1	674	1
Delhi	87 047		91 804	18	96 206	18	97 360	18	98 112	18
Himachal Pradesh	462		3 793	4	10 230	4	12 249	4	13 349	4
Tripura			2 356		3 660		7 605		8 105	
Manipur			2 768				6 252		6 252	
Pondicherry			6 707		6 707		6 707		6 707	

* Figures are from reports from the World Health Organization for 6 July and from Government of India notifications for August to February.

by 8 June. The spread of the epidemic from the 24th week onwards was one in depth and intensity in the areas already affected. Thus New Delhi, which had a total of 80 573 cases in June with 15 deaths, had 1000 cases in the first three days of June, 2796 on 6 June, 3830 on 7 June, 4718 on 8 June, with a peak of 6460 on 11 June, falling to 3057 on 16 June and 1761 on 22 June. Study of the daily incidence of influenza cases at the Lawley Hospital, Coonoor, for the months of May, June and July, shows a gradual increase from two cases on 2 June to 27 on 6 June, 120 on 11 June and a peak of 431 on 18 June. The intensity of infection in the early weeks of the pandemic cannot be assessed as no mechanism was available for collection of statistics on the disease at that time. The first consolidated data refer to the total number of cases from the commencement of the outbreak up to 6 July, or the 27th week. The cumulative figures for cases and deaths from 6 July 1957 to 8 February 1958 are given in Table 1. An analysis of these figures has shown that in the first seven weeks (i.e., up to 6 July), Mysore had had 52 %, Kerala 50% and New Delhi 88% of their total cases for 38 weeks, while Uttar Pradesh had had only 16%, Orissa 17%, Bombay and West Bengal 25% each and Bihar 3% only of their total cases. But by the 32nd week (i.e., up to 10 August, or in the 12 weeks since the start of the epidemic), most of the States had had 75% or more of cases, e.g., Assam 90%, Mysore 94%, New Delhi and Orissa 93% each. By the same date West Bengal had had 53%, going up to 63% by 7 September and 98% by 5 October only, and Uttar Pradesh 69%, going up to 85% by 7 September. The figures for Madras State in the return give 49% of total cases by 6 July, but according to a statement in the Legislature, it had had about 500 000 cases by then, finishing at 85% and going up to only 89% by 10 August. The main wave of influenza would thus appear to have swept across the country within a period of 12 weeks ending on 10 August 1957. The cases occurring subsequent to that date in all the affected areas represent the permanent infiltration of a new virus into the population, as distinct from its early massive pandemic attack.

Attack-Rates

By age-group

Tables 2 and 3 give the distribution of patients according to age-group, the one for May, June and July 1957 in the Lawley Hospital, Coonoor, and the other for June and July in the out-patient clinic attached to the Nutrition Research Laboratories, Coonoor. An interesting feature is that in both tables the maximum incidence percentage for June is in the 6-10-year group and for July in the 0-5-year group. It is not safe to draw any conclusion from this observation, unless figures from other countries and areas support the finding. The possibility exists that this phenomenon is due to

TABLE 2. AGE DISTRIBUTION OF 6220 INFLUENZA PATIENTS SEEN AT LAWLEY HOSPITAL, COONOOR, IN MAY, JUNE AND JULY 1957

Age-group (years)	May		June		July		Total	
	cases	%	cases	%	cases	%	cases	%
0- 5	6	4.8	769	16.1	385	*28.7*	1 160	18.7
6-10	16	12.8	871	*18.3*	233	17.4	1 120	18.0
11-15	9	7.2	590	12.4	114	8.5	713	11.4
16-20	18	14.4	680	14.3	146	10.8	844	13.6
21-25	26	*20.8*	553	11.6	125	9.3	704	11.3
26-30	9	7.2	444	9.3	85	6.3	538	8.6
31-35	13	10.4	240	5.0	85	6.3	338	5.4
36-40	11	8.8	229	4.8	47	3.5	287	4.6
41-45	0	0	131	2.7	30	2.2	161	2.6
46-50	9	7.2	122	2.5	44	3.2	175	2.8
51-55	5	4.0	45	0.9	15	1.1	65	1.04
56-60	0	0	55	1.15	22	1.6	77	1.2
61-65	2	1.6	13	0.27	2	0.15	17	0.3
66-70	0	0	12	0.26	3	0.22	15	0.2
71-75	1	0.8	2	0.04	0	0	3	0.05
76-80	0	0	2	0.04	0	0	2	0.03
Over 80	0	0	0	0	1	0.07	1	0.01
Total	125		4 758		1 337		6 220	

the school-going children becoming infected early in the epidemic and the pre-school children acquiring their infection later on from the older ones. All the data are in agreement as to the gradually diminishing incidence in the higher age-groups.

The age-group 31-35 years seems to be the dividing line between the high and low incidence. However, further statistical inquiry is needed to find out whether data from other areas support this finding. Is it that individuals born well after the 1918 pandemic—say in 1923, by which time the pandemic strain may have disappeared—were affected to a significantly greater degree during 1957 than those alive in 1918 and the succeeding five years?

By State

The incidence of the disease in the different States of India has been given in Table 1. If the incidence of the disease is worked out from the

TABLE 3. AGE DISTRIBUTION OF 467 INFLUENZA PATIENTS SEEN AT NUTRITION RESEARCH LABORATORIES, COONOOR, IN JUNE AND JULY 1957

Age-group* (years)	June		July		Total	
	cases	%	cases	%	cases	%
0- 5	37	10.0	23	*23.0*	60	12.8
6-10	81	*21.9*	12	12.0	93	20.0
11-15	68	18.4	9	9.0	77	14.3
16-20	54	14.9	8	8.0	62	13.3
21-25	34	9.2	10	10.0	44	9.4
26-30	33	8.9	15	15.0	48	10.3
31-35	11	3.0	4	4.0	15	3.2
36-40	16	4.3	2	2.0	18	3.9
41-45	10	2.7	9	9.0	19	4.0
46-50	10	2.7	3	3.0	13	2.8
51-55	4	1.0	2	2.0	6	1.2
56-60	11	3.0	1	1.0	12	2.5
Total	369		98		467	

* No cases were seen at ages over 60.

figures in that table in relation to the population of the various States according to the 1951 census figures, it is seen to vary from 0.4% in Rajasthan, Uttar Pradesh and Bihar, 0.6% in New Delhi, 0.7% in Andhra Pradesh, 0.8% in the Punjab, 0.9% in Madhya Pradesh, 1.0% in Orissa, 1.1% in West Bengal and Manipur, 1.3% in Tripura, 1.4% in Himachal Pradesh and 1.9% in Madras to the relatively high incidence of 2.1% in Assam and Kerala, 2.2% in Mysore and Andaman and Nicobar and 2.8% in Bombay. The figures reported, however, are likely to be much lower than the actual number of cases, while the 1951 census figures for population are also lower than actual ones for 1957.

By occupational group

The only occupational group that showed a distinctly higher than average incidence of the disease in many cities and towns was that of the medical and nursing personnel. In a large teaching hospital, for instance, cases occurred in 147 nurses (43%), 30 house surgeons (25%), 17 medical students (21%) and 33 other staff (6%). Patients in many towns and villages experienced great difficulty owing to the large proportion of medical persons who fell ill.

In closed communities

Fairly accurate data are available regarding the incidence of influenza in special groups, as, for example, in a European residential school at Coonoor over three successive years (Table 4).

TABLE 4. INFLUENZA CASES IN AN EUROPEAN RESIDENTIAL SCHOOL IN COONOR, 1956-58

Year	Date of reopening	Date of onset of first case	Duration of epidemic	Total of influenza cases	Total number at risk	Incidence (%)
1956	10 February	17 February	32 days	90	145	62.0
1957	13 February	17 February	67 days	66	168	39.2
1958	7 February	8 February	21 days	105	184	57.0

Laboratory studies on the 1956 and 1958 outbreaks in the school resulted in isolation of type A influenza virus from several children, the A/Netherlands/56 strain being involved in 1956 and A/Singapore/57 strain in 1958. Unfortunately, no intimation as to the 1957 outbreak was received at the time of its occurrence and it was therefore not investigated. It is not possible to decide whether it was due to a recurrence of the 1956 subtype or to a type B infection. The distribution of cases—66 over 67 days—is in contrast to those in 1956 and 1958. It is surprising that despite the wide prevalence of the 1957 pandemic in Coonoor, the school was not affected by the Asian virus in that year. A similar escape from the 1957 Asian epidemic was noticed in an orphanage within half a mile of the school where in 1956 there had been 95 cases of influenza out of a total of 113 persons. Strains isolated belonged to A/Eire/55, although A/Netherlands/56 strains were causing infection at Coonoor in the same period. There was no outbreak of influenza in the institution in 1957. In February-March 1958, all persons in the orphanage were inoculated with the Coonoor influenza virus vaccine, and to date they have remained free from infection with the Asian virus strains.

It is worth while to compare the attack-rates observed in institutions and other closed communities in 1957 with those in the same or similar institutions in earlier years and with different strains and types of virus. Table 5 gives the data for 19 outbreaks occurring in India and in ships arriving in India for the period 1950 to 1958. While it may not be safe to draw general conclusions, it is interesting to note certain trends. A new virus strain causes sharp outbreaks limited to three or four weeks, with attack-rates varying from 8% to 15%. The Asian strains do not appear to be more invasive in adult populations or even in children than the Liverpool,

TABLE 5. ANALYSIS OF 19 OUTBREAKS OF INFLUENZA IN DIFFERENT GROUPS BETWEEN JUNE 1950 AND FEBRUARY 1958

Period	Area	Duration of outbreak (days)	Population at risk	Number of cases of influenza	Incidence (%)	Type or strain responsible
June 1950	St. Thomas Mount, Madras	17	600	52	8,6	Type A1
August 1950	Yedapalli Village, Coonoor	28	795	91	11.4	Liverpool *
February 1951	s.s. *Chusan*	17	352	50	14.2	Type A1
October 1951	Barahapjan, Assam	22	3000	422	14.0	Type A1
November 1951	Borstal School, Palamcottah	18	750	about 100	13	Type A1
December 1952	Borstal School, Palamcottah	18	637	175	27.5	Type B
July 1953	Raipur	19	750	38	5.1	Type A1
February-March 1956	Orphanage, Coonoor	16	113	95	84.0	A/Eire/55 *
March 1956	Residential School, Coonoor	32	145	90	62.0	A/Netherlands/56 *
March 1957	Residential School, Coonoor	67	168	66	39.2	? Type B
February 1958	Residential School, Coonoor	21	184	105	57.0	A/Asia/57 *
May 1957	s.s. *Rajula*	7	about 1800	254	14	A/Asia/57 *
May-June 1957	Lovedale School	30	533	255	47.8	A/Asia/57 *
June 1957	Military establishment	21	about 3000	333	11	A/Asia/57 *
June-July 1957	Tea estate 1	52	about 4000	1486	37	?
June-July 1957	Tea estate 2	76	about 1200	500	41	?
January 1958	Tea Estate 2	15	about 1200	about 625	52	A/Asia/57 *
September 1957	s.s. *Mathura*	11	83	16	19.2	?
Septembe 1957	s.s. *Maidan*	6	87	9	10.3	A/Asia/57 *

* Virus isolated

A/Eire/55, or A/Netherlands/56 strains. The highest attack rates—84% with A/Eire/55, 62% with A/Netherlands/56 and 57% with A/Asia/57, the last two in the same European residential school—are found in children between the ages of 6 and 15 years. The crowded conditions obtaining in steamers do not seem to increase the attack-rates. The higher susceptibility of children generally, regardless of the virus strain, is well shown in the table. The high attack-rates of 37.1%, 41.7% and 52.0% for two tea estates in the Nilgiris are probably caused by the alternation of working conditions from close contact in the labourers' quarters at night to work in the open air in the day involving exposure to inclement weather and cold associated with a high elevation (6500-7500 feet, or 1980-2290 m).

Mortality Rates

The recorded figures for mortality due to influenza during the 1957 pandemic in India have been given in Table 1. For the period of 38 weeks from 19 May 1957 to 8 February 1958, there were 4 451 785 cases of influenza with 1098 deaths in the whole of India. With a population of 360 million according to the 1951 census, this gives an attack-rate of 12 366 and a mortality rate of 3 per million of population. The case-fatality rate for the whole of India works out to 242 deaths for every million cases. It has been pointed out earlier that the attack-rates varied from a low of 0.4% or 4000 per million population in Rajasthan, Uttar Pradesh and Bihar to a high of 2.8% or 28 000 per million in Bombay. The mortality rates and case-fatality rates for the various States in 1957 are given in the left-hand part of Table 6. There are some unusual features in the distribution of mortality in adjacent States. The case-fatality rates bring out particularly clearly the differences in behaviour of the disease in different areas. It would be interesting to see whether, in other countries as well, areas with high influenza mortality are found side by side with areas with low mortality.

Table 6 also gives the figures for influenza mortality in the various provinces in India during the 1918 pandemic, with the death-rates per 1000 of the population and the percentage of deaths in the age-group 20-40 years in relation to total deaths. It must be pointed out that the areas coming under the States in 1957 are not the same as those of the provinces in 1918, though sometimes bearing the same name. Despite this anomaly, it is perhaps worth noting that Bengal had the lowest mortality rate (8.5 per 1000) in the 1918 pandemic but the highest (1539.5 per million) during 1957; indeed West Bengal, with 7.2% of the total population of the country, accounted for only 6.4% of all influenza cases but for 40.5% of all influenza mortality. No convincing explanation of the differences shown by the various States with regard to mortality is available. The figures given in Table 6, however, do illustrate the tremendous difference between the 1918 and 1957 pandemics in their effect on mortality.

TABLE 6. MORTALITY FROM INFLUENZA IN INDIA IN THE PANDEMICS OF 1957 AND 1918 *

1957 pandemic						1918 pandemic			
State	population at 1951 census (millions)	total influenza cases	total influenza deaths	influenza death-rate per million population	Case-fatality rate per million cases	Province	total influenza deaths	influenza death-rate per thousand population	percentage of deaths in 20-40-year age-group among total deaths
Andhra Pradesh	32.2	220 138	28	0.87	127.2				
Assam	9.0	191 058	7	0.78	36.6	Assam	111 340	18.6	27
Bihar	38.9	155 146	18	0.46	116.0				
Bombay	47.8	1 323 975	315	6.59	237.9	Bihar and Orissa	709 976	20.5	23
Kerala	13.6	289 265	9	0.66	31.1	Bombay	1 059 497	54.9	23
Mysore	19.0	416 986	70	3.68	167.9				
Madras	30.0	583 107	75	2.50	128.6	Madras	682 169	16.7	25
Madya Pradesh	26.1	245 471	13	0.50	53.0				
Orissa	14.6	151 398	12	0.82	79.3	Central Provinces and Berar	924 949	66.4	28
Punjab	16.0	121 360	9	0.56	74.2	Punjab	898 947	45.4	26
Rajasthan	16.0	58 346	10	0.63	171.4	United Provinces of Agra and Oudh	2 034 257	43.4	28
Uttar Pradesh	63.2	270 661	64	1.01	236.5				
West Bengal	26.1	289 048	445	17.05	1539.5	Bengal	386 572	8.5	52
Delhi	1.7	98 112	18	10.59	183.5	Delhi	23 612	56.6	26
Himachal Pradesh	0.98	13 349	4	4.08	299.6				

*** Owing to integration and redistribution, the present States are not the same as the Provinces of 1918, though the names are common in many instances.**

Second Attacks

The only instance of two outbreaks both proved to be due to Asian virus by isolation of the strains and by serological investigations was in a regimental centre. In June 1957 an influenza outbreak in that centre affected over 330 persons out of 3000 at risk and in November there was another outbreak with over 112 cases in seven days. On each occasion, the Asian virus was isolated at Coonoor from two of the throat washings.

Two outbreaks of influenza within a relatively short time have also been reported in other areas; in some instances, these were proved to be due to different virus types, and in others virus isolations were not made during one or the other of the two outbreaks. Inquiry at the time of the second outbreak frequently revealed that most patients had escaped infection in the earlier outbreak. However, second attacks in individuals have often been reported, both in the May-August 1957 period and later. The concurrent presence of viruses of the Asian group as well as of type B makes it difficult to decide how far the second attack is due to the same type of virus as that causing the first.

Clinical Features

Nausea and vomiting were present in an unusually high percentage of cases in 1957 in most areas in India. While they did not pose a serious threat to life in the majority of cases, in a few patients vomiting gradually increased in frequency and led to deepening stupor and death. Bradycardia was a constant feature. Jaundice appeared in a very small number of patients. Epistaxis was reported in about 10% of cases, followed in a small number of cases by haemetemesis, melaena and death. These features suggest a possibility that the 1957 virus had a specially damaging effect on the liver.

Reports were received from many areas of the presence of a dysenteric condition simultaneously with or immediately following the main outbreak of influenza. No laboratory studies were made on the etiology of the dysentery, but the reports came from widely scattered areas in Kerala, Madras and Uttar Pradesh as well as outside India. It was diagnosed in some areas as gastric influenza or influenzal dysentery.

Another feature of the pandemic was the frequency of signs and symptoms related to the nervous system. Clear-cut evidence in support of the production of encephalitis or meningitis by the virus directly is not available; but signs and symptoms included stiffness of the neck, stupor, delirium, complete disorientation, mental depression and boisterous and violent behaviour requiring physical control of the patient. Udani et al. (1957) reported that 21 children out of 420 (5%) admitted for influenza showed evidence of cerebral and meningeal involvement, 5 predominantly meningitic, 5 encephalitic and 11 a mixed type, and that more than half of them died.

The frequency of involvement of the lungs during influenza is rather difficult to decide on a purely clinical basis. It is likely to be high in cases admitted to hospital. In a small series of 25 patients subjected to radiological investigation at Lawley Hospital, Coonoor, the lung picture showed some abnormality in 14 cases and pronounced changes in six of these. As the patients were selected for investigation on account of the severity of disease, the findings are not applicable to the ordinary run of cases. Gadekar (1958), working at Irwin Hospital, New Delhi, studied 412 pictures taken at random from 1199 cases admitted on the criteria of fever above 104°F (40°C), marked asthenia, persistent vomiting and/or diarrhoea, haematemesis, epistaxis and symptoms referable to the chest. Of these, 141 (37%) showed changes. Further classification of the 141 positive photographs revealed 45 (32%) with early inflammatory changes confined to bases, 36 (26%) with generalized lesions suggestive of bronchiolitis and bronchopneumonia, 45 (32%) with lobular consolidation and 15 (11%) showing segmental and lobar distribution. Many cases showed few or no clinical symptoms in the presence of striking radiological changes. Two interesting observations are recorded by Gadekar. The incidence of lung lesions increases with advancing age of the patients, being 29% in 0-14-year-age-group, 34.7% in 15-30-year group, 54.7% in 31-50-year group, and 100% in the six patients aged over 50. He also noted that the incidence increased during the evolution of the epidemic, being 21 % in the week 7-13 June, gradually going up to 22%, 40% and 57.7% in the following weeks. Yodh et al. (1957) radiographed 121 cases admitted at the Arthur Road Infectious Hospital, Bombay, and found 38 of them showing changes. Patchy consolidation, collapse and consolidation with collapse accounted for 24 of them (20 % of the total radiographed).

Another important finding by Yodh et al. was the evidence of myocarditis in 16 out of the 123 cases in which electrocardiograms were taken. Though its incidence was higher (5.7%) in the group of severe cases, it was demonstrated in the mild (3.3%) and moderate (4%) groups also. The danger of going back to work too soon after an attack of influenza is obvious from these findings.

Organisms Isolated and Pathological Observations

The fatal cases at Coonoor were too few for statistical study. The first fatality at Lawley Hospital was in a young girl aged 12 years admitted on 12 June 1957 with a history of fever for one day only, but in a highly toxic state, with delirium and persistent vomiting; she died the same day. Her throat swab yielded *Streptococcus haemolyticus* as well as *Streptococcus non-haemolyticus (Enterococcus)* on culture and A/Asia/57 virus on egg inoculation. *Diplococcus pneumoniae* was obtained on culture from a very

serious case whose recovery was unexpected. Coagulase-positive *Staphylococcus aureus* was found in several cases of varying degrees of severity. *Haemophilus influenzae* was seen only once, in a case with severe bronchopneumonia. Other organisms isolated from about 30 cases of influenza studied bacteriologically included, in addition to the bacteria mentioned above, *Bacillus proteus*, *B. lactis aerogenes*, coliform and diphtheroid organisms and a particular Gram-negative organism, not fermenting any of the sugars, that could be labelled *B. faecalis alkaligenes* or *H. bronchisepticus*. It has the unusual property of haemagglutinating fowl as well as guinea-pig cells to high titre when present in egg fluids or even in suspensions taken from culture tubes. It is a particularly troublesome contaminating organism, being insensitive to sulfonamide compounds and all the antibiotics tested against it so far. During the pandemic wave, no studies could be undertaken on the sensitivity of the bacteria to antibiotics. But early in 1958, of 25 strains of *Staphylococcus aureus*, 8 were found to be resistant to penicillin in concentrations over 10 units per ml. All the 8 strains were found resistant to streptomycin also in concentrations of 20 μg and above per ml. Both penicillin-sensitive and penicillin-resistant strains were found to be destroyed equally well by iodine in a dilution of 1 in 20 000. Out of the 25 strains, 12 were isolated from cases of influenza and two of these were resistant to penicillin in concentrations as high as 3125 units per ml.

Post mortem notes kindly made available to me by the medical officers concerned cover four cases only. Generalized congestive changes were evident in the brain, in the mucosa of the stomach, and in two cases in the spleen and kidneys. Patchy congestion in the lungs was present in all four, with pleural adhesions on both sides in two cases and four ounces of blood-stained fluid in the left pleural cavity in one. The liver was congested in one and showed greyish-yellow patches in two others.

The cause of death in the majority of patients seems to be related to the development of pneumonitis, frequently with haemorrhagic changes. In two cases where severe vomiting supervened after the patient became afebrile 48 hours after onset of illness, the blood urea was raised to 45 mg% and 60 mg% respectively the day before death. It is not clear to what extent the changes in the liver, brain and other organs are due to the severe anoxaemia resulting from extensive penumonitis. Histopathologica examination of the liver sections and liver biopsy specimens showed degenerative and fatty changes quite different from those in infective hepatitis and compatible with the results of continued lack of oxygen.

Virus Isolation

In previous years, throat gargles from suspected cases were collected only from the Nilgiris district and brought packed in ice to the Pasteur Institute at Coonoor for storage in the deep-freeze within a few hours and

for subsequent isolation of virus. During 1957, in addition to this, collections had to be made from distant places such as Madras and Kolar Gold Fields. Conditions of collection, storage and transit of specimens varied widely, from those associated with boarding steamers under quarantine in a rough sea by rope-ladders and transporting specimens in hot weather in crowded railway compartments to the almost perfect conditions of choosing patients from a well-ordered hospital and storing specimens immediately in the deep-freeze.

Specimens were collected from patients at the Institute itself not only during the epidemic but also during periods when there was no influenza; however, only four virus isolations have been made from over 30 specimens collected at such periods. From January 1957 until July 1958, 43 virus isolations were made from throat gargles. The first isolation was in January 1957 during a small outbreak at Coonoor, and the strain was found to belong to the A/Netherlands/56 subtype. About 60% of the remaining 42 strains have been tested and found to belong to the A/Asia/57 subtype.

It was found that the newly isolated strains differed considerably from the previous A and A1 strains, not only antigenically but also in biological characteristics. They grew with difficulty in the early egg-passages, gave low haemagglutination titres with both fowl and guinea-pig cells and did not show the characteristic O phase. Previous studies at Coonoor had shown that normal fowl sera did not generally contain non-specific inhibitors against the A1 strains, although against a few strains low titres of the order of 1 : 8 or 1 : 16 were seen. In contrast, they were inhibited by normal rabbit sera in dilutions of 1 : 256 and even higher. Antisera prepared in fowls were, as usual, used for testing the Asian strains in 1957. Very erratic results were obtained that led to further studies on their possible causation. It was then found that some of the 1957 strains were totally insensitive to the non-specific inhibitors in the sera of all animals tested, unlike the A1 strains; but other Asian strains were highly sensitive not only to the inhibitors in normal human, guinea-pig and rabbit sera, like the A1 ones, but also to those in normal fowl sera, unlike the A1. The totally insensitive Asian strains resemble the HVJ or Sendai virus in this respect, as is shown in Table 7.

Another unusual characteristic of some of the Asian strains is their reaction to ether treatment. Andrewes & Horstmann (1949) demonstrated the effect of ether in inactivating the influenza virus. Hoyle (1952) concluded that ether is able to break down the virus into its constituent parts such as RNA, body protein and lipoid coat. He found an increase in the haemagglutinating titres of the virus against guinea-pig cells, following the action of ether. Henle (1953) showed that ether treatment of virus results in a diminution of the haemagglutination titre with fowl cells. These results were regularly obtained in experiments at Coonoor, using the Liverpool, Scandina-

TABLE 7. STRAIN SUSCEPTIBILITY TO INHIBITORS IN NORMAL ANIMAL SERA

Strains	Inhibition titres of sera from :			
	fowl	guinea-pig	man	rabbit
A/Asia/Par (untreated)	0	0	0	0
A/Asia/Par (thiomersal-treated)	0	0	0	0
A/Asia/Kolar VI (untreated)	128	512	1024	256
A/Asia/Kolar VI (thiomersal-treated)	64	128	128	128
A/Asia/Palaniamma (untreated)	32	32	64	32
A/Asia/Sarojini (untreated)	0	0	0	0
A/Asia/Tara Nalvani (untreated)	0	0	0	0
A/Asia/Vichare (untreated)	64	32	128	64
A/Asia/Kolar II (untreated)	64	32	128	64
A/Asia/Bangalore (untreated)	64	128	128	64
A/England/51—Liverpool (thiomersal-treated)	8	16	256	64
A/Netherlands/56—Shirley (untreated)	8	64	256	256
A/Netherlands/56—Shirley (thiomersal-treated)	8	32	64	64
B/Crawley (untreated)	0	16	128	32
B/Nanji (untreated)	0	8	16	16
Sendai (untreated)	0	0	0	0

vian, A/Netherlands/56 and other strains. Some of the Asian strains reacted quite differently, giving increased haemagglutination titres with fowl cells. After treatment with equal parts of ether, at 0°C and room temperature as well as at 37°C, the haemagglutination titres with fowl cells were 4-16 times greater than the pre-treatment titres in the case of the Par strain sent from Singapore and the Kolar VI strain isolated from Mysore. The guinea-pig cell titres showed even higher rates of increase. On further egg-passages, the degree of increase of titre diminished, though even after five passages, Par showed a threefold and Kolar VI a sixfold rise in titre after treatment. Many of the Asian strains as well as all the well-adapted A and A1 strains showed, on the contrary, the usual fall in titre with fowl cells observed by Henle.

The strains were tested for their sensitivity to the lethal action of iodine observed with other A and A1 viruses. They were found to be destroyed by iodine in the same dilutions as were effective earlier. Some strains of the virus isolated elsewhere in India (Bombay, Trivandrum and Bangalore) were kindly sent to me by the workers concerned for comparative study. They showed much the same features—low haemagglutination titres,

sensitivity to fowl serum inhibitors, and varying reactivity to immune sera. A strain isolated by Professor Ananthanarayanan at Trivandrum, labelled RAMT, resembled the Kolar VI strain very closely in its high degree of sensitivity to inhibitor.

Another strain that deserves attention is one isolated by Dr V. N. Krishnamurthy of the Vaccine Institute, Bangalore, from the cerebrospinal fluid of a young girl aged 10 years from Shimoga, Mysore State. She had a previous history of epilepsy, the attacks being of the *petit mal* type. Her illness started with fever after returning from school on 1 June 1957. She developed convulsions on 2 June and remained in a semi-comatose condition until the morning of 4 June. The attending physician obtained the spinal fluid from a lumbar puncture on 2 June and delivered it, packed in ice, to the Vaccine Institute, Bangalore. Amniotic inoculation on eggs yielded a fluid haemagglutinating chick cells. After two further allantoic passages, the fluid was sent to Coonoor for virus identification. The strain was found to be inhibited by antisera against the typical Asian strains. Specific antiserum was prepared in fowls with the material, and cross-inhibition tests showed no difference between it and the Par, Kolar VI and other 1957 viruses. In view of the reported isolation of the HVJ or Sendai virus from cerebrospinal fluid, it was tested against anti-Sendai fowl serum but with negative results. The strain did not show any evidence of special neurotropism on intracerebral inoculation into mice. The patient's epileptic attacks, previously of the *petit mal* type, have become more frequent, severe and convulsive, according to a report from her physician in April 1958. It is not clear whether the epileptic state of the patient has anything to do with unusual isolation of the influenza virus from cerebrospinal fluid. So far as I am aware, isolation of the influenza virus from cerebrospinal fluid from patients has not been reported. Brown, Muether, Pinkerton & LeGier (1945) isolated a virus from the spinal fluid of a patient in January 1944 during an outbreak of influenza at St. Louis, Mo., but as it was not inhibited by known influenza A or B antisera, it has not been accepted as influenza virus. In future, it would be advisable for the cerebrospinal fluid as well to be used for egg inoculation when virus isolation is attempted from cases showing involvement of the central nervous system.

While isolation of the virus from specimens of throat gargles or swabs was satisfactory, the experience with material collected from patients *post mortem* was not encouraging. Lungs and other organs removed *post mortem* from fatal cases of influenza were sent by post or courier from Madras and Secunderabad through the kind co-operation of the medical officers concerned. Amniotic fluids from some of the eggs inoculated with tissue extracts haemagglutinated fowl and guinea-pig cells, as did allantoic fluids obtained on further passage. However, the fluids showed bacterial growth on culture. It was found impossible to get rid of the bacteria despite treatment with sulfonamide products, antibiotics and other agents

such as ether and benzalkonium chloride. An organism found with great frequency in these materials, and mentioned earlier, was a Gram-negative bacterium that did not ferment any of the usual sugars and could well be labelled either *Bacillus faecalis alkaligenes* or *Haemophilus bronchisepticus.* It is also of interest to note that the cerebrospinal fluid from one of the cases in which this organism occurred yielded on amniotic inoculation a fluid haemagglutinating fowl and guinea-pig cells. It is not possible to establish the presence of a virus in these materials in view of the finding that the above bacterial organism itself causes haemagglutination of both fowl and guinea-pig cells, when present in infected egg fluids or in suspensions from culture tubes on certain media.

Serological Studies

Paired sera from patients, deactived at 56°C, were tested against the Par strain in haemagglutination-inhibition tests and found to give few positive results. Clinically typical cases as well as some others from whom the Asian virus was isolated showed no significant rise in antibody titre. The use of local strains had occasionally given better results in previous epidemics, and therefore the sera were retested against strains recently isolated from Coonoor, Madras and Mysore. In the very first experiment, 10 paired sera were used against Par, Kolar VI, the Coonoor strain of A/Netherlands/56 and two type B viruses. None of them showed rise in titre against the type B viruses or the A/Netherlands/56 strain. Two patients gave a fourfold rise in titre against the Par strain while six patients, including the two reacting with Par, showed a diagnostic rise in titre against the Kolar VI strain, two of them with a 16-fold increase. However, it was found difficult to utilize the Kolar VI as a routine diagnostic strain because it was sensitive to the action of non-specific inhibitors present in varying degrees in the patients' deactived sera. Complement-fixation tests had the disadvantage that they could not differentiate between infections with previous A1 strains and those with the current Asian strains. Utilizing a reactive strain like Kolar VI in diagnostic tests was possible only after the removal of inhibitors. This entailed time-consuming studies on various methods, many of which, though useful in the past, proved inadequate with the Asian strains. Ultimately it was found that the use of potassium periodate according to a method recently advocated by Jensen (personal communication—1957) was satisfactory, particularly with human sera. Rarely, it gave a flocculent precipitate with fowl sera, removing most of the antibodies and thus giving erratic results. Parallel tests were carried out on deactived sera, sera treated with cholera filtrate and sera treated with periodate. A drop in antibody titre was noticed following periodate treatment, specially in immune sera, after a first injection; but there is no doubt that the most clear-cut results were obtained with the periodate-treated sera, even

with highly inhibitor-sensitive strains like Kolar VI. Heat-deactived sera from 39 patients were tested against different antigens in the haemagglutination-inhibition test during the early period of the epidemic. A minimum of four antigens was used in any of the tests, though the particular strains representative of types or subtypes were not always the same on different days. The strains used were Par, Kolar VI, Singapore, Mangalian and Palaniamma among the Asian strains, Shirley for the A/Netherlands/56 group, and A/Liverpool/51, B/Govindaraj/53, B/Nanji/54 and B/Crawley. Seven of the sera did not react with any of the antigens, four reacted against B antigens, two with A/Netherlands/56, eight with Par and 13 with Kolar VI. In this group of sera, all the four pairs reacting with a fourfold or greater rise in titre against the B antigens showed a similar or greater rise against the Asian strains as well and probably represented simultaneous infections with Asian and type B viruses. The Kolar VI antigen yielded the highest number of positive results but its great sensitivity to inhibitors detracted from the value of the findings. Parallel tests were carried out on sera after heat-deactivation and treatment with cholera filtrate and potassium periodate. Results with cholera filtrate had been satisfactory in previous years but were very erratic this time. With some sera, the results were clear-cut but with others, inhibitors apparently were not removed by the cholera filtrate. Several batches of the filtrate were tried but with the same erratic findings. Potassium periodate treatment gave more satisfactory results, particularly with human sera.

Sera from 91 patients, including some already tested after heat-deactivation, were tested after periodate treatment. This group represented more areas in the country than the 39 heat-deactivated sera. Of the total, 22 did not react with any of the antigens. Twenty-six gave a fourfold or greater rise in titre against the Kolar VI antigen and 4 out of 57 against the Par antigen, while 22 out of 85 specimens gave a diagnostic rise with the type B antigens. Out of these 22 cases, 15 reacted to B antigens only, while 7 reacted to both B and Asian or other A strains. These figures accord closely with those given above with heat-deactivated sera for these apparently concurrent infections with A and B viruses. With the A/Netherlands/56 strain, 6 sera out of 60 gave a diagnostic rise in titre, and 3 of the 6 reacted only with that strain. Similarly with Liverpool strain, 12 sera gave a diagnostic rise in titre out of 76 tested, 3 reacting only with Liverpool strain. To what extent these findings can be interpreted as due to infections with the 1951, 1956 and 1957 A strains singly or severally remains to be decided. However, for the results with the B antigens it can be safely assumed that about 17% of the sera tested came from patients with type B infection alone and 8% from those suffering from concurrent infections with types A and B. While the results of the serological tests leave no doubt about the occurrence of type B infections in India in 1957, they could not be proved by isolation of type B virus.

It has been pointed out already that the Kolar VI antigen yielded a greater number of positive results than the Par in haemagglutination-inhibition tests—33% against 20% in the heat-deactivated sera and 28% against 7% in the periodate-treated sera. It is not easy to explain why this should happen. One suggestion is that though antigenically similar to Par, Kolar VI is more sensitive to the action of non-specific inhibitors as well as of specific antibodies, perhaps an example of P-Q phase variation. Another possibility is that they are distinctly different strains in many respects, with some antigenic complexes only in common.

An interesting observation during the serological tests was that two patients reacted only to one particular Asian strain in each case and not to Par, Kolar VI, or Singapore. One was a patient from the Lawley Hospital, Coonoor, whose sera showed no rise in titre against Par, Kolar VI or Singapore strains in the Asian group or against A/Netherlands/56 or the type B strains but reacted with a fourfold rise against the strain Mangalian isolated from one of the cases in the s. s. *Rajula*. The second patient was an estate worker from whom an Asian virus was isolated during an outbreak in January 1958. Her sera reacted only with her own virus but not with Par, Kolar VI or a strain isolated from another patient in the same outbreak. If Kolar VI is assumed to be the Asian virus in P phase in view of its high reactivity, it is difficult to explain why the sera from these two patients should not react with it but with other strains. The strain Mangalian was one of three viruses tested at the World Influenza Centre in London with homologous ferret sera. All three were found to be Asian viruses in the Q phase. But tested against periodate-treated fowl antisera prepared at Coonoor against Par and Kolar VI strains, the three strains differed considerably.

The strains Mangalian (A/India/7/57) and Abdul Muthali (A/India/8/57) are inhibited equally by Par and Kolar VI sera, though Abdul Muthali is inhibited to titres of 1 : 1024 but Mangalian to 1 : 128 only. The third strain, Tara Nalvani (A/India/9/57), is not inhibited by the Par serum but is sensitive to the Kolar VI serum to a titre of 1:128. Another strain, Sarojini, appears similar to Tara Nalvani, being inhibited by Kolar VI serum to a titre of 1 : 32 and not being inhibited at all by the Par serum. Only two strains, both isolated at Bangalore, show a higher sensitivity to Par than to Kolar VI serum; but the difference is not significant in one, while the other—which is the strain isolated from the cerebrospinal fluid of the epileptic patient mentioned earlier—is inhibited to a titre of 1 : 128 by Par but of only 1:16 by Kolar VI serum.

These observations on the variation in sensitivity to inhibitors and antibodies seen among the Asian strains find support from other workers in China as reported by the World Health Organization, in Malaya as confirmed by Dr J. R. Andy in a personal communication, and in India as reported by Professor Ananthanarayanan (1958).

The effect of ether in increasing the haemagglutination titres of some of the Asian strains against fowl cells has already been mentioned. Sera from two fowls, both immunized with Par strain, were tested at the same time with Par and Kolar VI antigens treated with thiomersal or ether. The antigens were all adjusted to eight haemagglutinating units on the basis of the titres obtained after treatment with thiomersal or ether. The results are as follows:

Sera	*Antigens*			
	Par (thiomersal)	*Par (ether)*	*Kolar VI (thiomersal)*	*Kolar VI (ether)*
Fowl 11	512	4096	1024	>8192
Fowl 43	2048	8192	2048	>8192
Heat-deactivated human serum	8	128	128	512
Periodate-treated human serum	8	8	8	8

The Par strain that is totally insensitive to non-specific inhibitors is here shown to become sensitive to inhibitors and also to specific antibodies in greater degree after ether treatment. The Kolar VI strain, already sensitive to inhibitor, becomes more so on ether treatment. It becomes difficult to resist at this stage the temptation to indulge in a speculative hypothesis regarding the structure of the Asian virus. Is it likely that all the peculiarities of its behaviour are due to an " armoured state "? If we can imagine the Asian virus donning, in the final stages of its production, a non-reactive, protective, incomplete surface-coating, it is easy to explain its high infectivity, low haemagglutinating capacity, poor antigenicity, low reactivity to specific antibodies, insensitivity to inhibitors and erratic behaviour in elution. Ether apparently removes the coating partially or fully and thus causes an increase in haemagglutinating capacity, reactivity to antibodies and sensitivity to inhibitor. By removal of the protective coat, the infectivity of the virus is lost because it is more open to the destructive action of its environmental conditions. As the strain moves through the population, the " armour " gets worn out or stripped in varying degree and we get a series of strains with the same antigenic core but differing widely in biological characteristics. Finally the armour is completely removed and the virus, devoid of its protection, is unable to resist the hostile influence in nature and is effaced. The localized outbreaks and periodic epidemics may be caused by strains in the partially protected phase while a pandemic is initiated by a fully " armoured " virus.

Preparation of Asian Influenza Vaccine

The unusually rapid and extensive spread of influenza in Asia in the early months of 1957 indicated the possibility of its being due to a new strain or subtype. It was realized that vaccines prepared from older and

mouse-adapted strains might therefore be ineffective, and if vaccine was to be prepared, the etiological strains had to be obtained. A representative strain isolated in Malaya and labelled Par was flown out to India, well packed in a CO_2-ice flask, and inoculated into eggs on 26 May at Coonoor. It was successfully established in eggs and the first consignment of material from it was sent to the Armed Forces Medical College, Poona, by 30 May for vaccine production there. Later on, it was distributed to other vaccine production centres and laboratories in India.

A committee was set up under the chairmanship of the Director General of Health Services, New Delhi, to consider the various problems concerned in the production of influenza vaccine and its use. A target production of 100 000 doses of vaccine was decided on, out of which the Coonoor Centre had manufactured 55 000 doses by 31 January 1958.

Since influenza had spread all over India by the first week of June, within three weeks of its introduction into the country, and since the first massive wave of infection had spent itself by 10 August, the vaccine could hardly receive a fair field trial, as the earliest batches were not ready until July.

Other Prophylactic and Therapeutic Measures

Experiments carried out in India before 1957 had shown that iodine was effective in the laboratory in destroying different strains of influenza virus, various preparations such as Mandl's paint, Lugol's solution and tincture of iodine being used. Laboratory experiments with the new Asian strains gave identical results. Research was in progress on the details of the action of iodine when the advent of the 1957 pandemic precipitated trials of its prophylactic and therapeutic value in human beings. In view of the rapid spread of the pandemic and of the urgent necessity to take protective measures, it was not possible always to insist on the use of control groups or, consequently, on as accurate an assessment of the results of field trials as would otherwise have been desirable.

Early in the pandemic, however, controlled trials were carried out; these have been reported elsewhere by Menon & Shaw (1957). Among the uncontrolled trials worthy of mention was one in a military hospital where 189 cases were reported in the first three days of an outbreak in June. Starting on the morning of the fourth day, the throats of all those at risk were painted twice daily with Mandl's paint. There were 144 further cases that day and a steady drop to 18, 6, 5, 1, 2 and 1 cases on subsequent days. Similar results were obtained in a further outbreak in November. Mention may also be made of use of Mandl's paint among 183 persons on a tea estate, of whom only five (2.8%) developed influenza, as against 689 cases in 4647 untreated persons (14%) on the same estate.

The use of iodine in the treatment of influenza gave the best results in severe cases, to whom 1-3 doses of 10 ml of colloidal iodine were generally administered intravenously. In several such cases, treatment was followed by a rapid drop in temperature and the disappearance of toxaemia. In mild cases, however, it has not been possible to show statistically that the results of iodine treatment are superior to those obtained in control groups given placebo injections or antibiotics. The simultaneous use of antibiotics and iodine does not apparently interfere with the action of either.

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It is obviously impossible to compile a report of this nature without the assistance of scores of individuals, institutions and administrations in supplying statistical information, diagnostic materials, special reports, laboratory and radiological findings and expert technical advice; it is equally impossible to mention all of them individually, but I would take this opportunity of expressing my grateful appreciation to them.

The studies on influenza the results of which are presented above owe their inspiration to the Government of India, which set up the Influenza Centre at the Pasteur Institute, Coonoor, in 1950. The help and assistance that have always been forthcoming from the Government of India have been increased during 1957, thanks to the Director General of Health Services, New Delhi, and to the Indian Council of Medical Research. Thanks are also due to the Director General, Armed Forces Medical Services, India, for the close co-operation received from the three military services.

The assistance rendered by the health officer and assistant health officer of the Port of Madras was of great value in the investigations on patients on board the quarantined steamers and that by the airport health officer, Madras, in the receipt and transmission of delicate biological materials.

The major part of the studies has been carried out in the State of Madras and was made possible only by the help afforded by the successive directors of medical services and the directors of public health, by the various officers in the medical colleges at Madras and Madurai, by the Director of the Institute of Venereology, General Hospital, Madras, by the Director, King Institute, Guindy, and by the district medical officers and officers of the Health Department.

The medical officers of the Lawley Hospital at Coonoor, the Military Hospital at Wellington, the Cordite Factory Hospital at Aruvankadu, the Lovedale School and Infectious Diseases Hospital at Ootacamund and various tea estates, educational and other institutions deserve special mention and thanks for their services in carrying out prophylactic and therapeutic trials with iodine among patients and contacts.

It is difficult to express adequately my indebtness to the Director, medical colleagues and scientific staff and members of the Pasteur Institute, Coonoor, for advice and technical assistance, and in particular to the members of the staff of the Government of India Influenza Centre and Vaccine Production Unit.

RÉSUMÉ

Le début de l'épidémie de grippe dans l'Inde coïncide avec l'arrivée en rade de Madras, le 16 mai, d'un navire qui avait quitté Singapour le 9 mai 1957 et avait été dirigé sur

Madras — au lieu de Nagapatam — en raison de l'épidémie de grippe sévissant à bord, frappant 254 personnes en 7 jours. Le bateau resta en quarantaine au large de Madras, et une équipe médicale donna les soins médicaux que demandaient 44 cas en pleine évolution. Des produits de lavage de gorge prélevés sur des malades les 16 et 17 mai furent envoyés à l'Institut Pasteur de Coonoor, repiqués sur œuf, et la première souche de virus asiatique fut isolée le 22 mai. Quatre des infirmières ayant soigné les malades du bateau tombèrent malades au bout de 48 heures. Le débarquement de plusieurs centaines de passagers le 21 mai, puis d'un autre navire le 28 mai, fut probablement à l'origine de la pénétration de la grippe dans la Province de Madras. D'autre part, les premiers cas étaient signalés à Bombay le 21 mai, à Calcutta la même semaine — 1000 cas et 2 décès au cours de la 22e semaine de l'année. Il semble que ces trois ports aient été infectés indépendamment par mer ou par air. Une carte indique le cheminement de l'épidémie qui, en 6 semaines envahit le sous-continent indien. Il faut noter qu'au début de 1957 une grippe à virus B sévissait dans l'Inde sous forme de poussées localisées, et que, dès l'arrivée de la grippe asiatique, les deux virus se propagèrent conjointement dans certaines régions, ainsi qu'en témoignent les épreuves sérologiques.

Des tableaux indiquent la répartition par groupes d'âge, parmi les malades d'un hôpital de Coonoor. Le pourcentage maximum, en juin, se trouve dans le groupe de 6-10 ans, en juillet dans celui de 0-5 ans. Ce sont peut-être les écoliers qui, infectés les premiers, ont contaminé les groupes d'âge inférieurs. La fréquence des cas nouveaux diminue dans les groupes d'âge supérieurs.

La répartition des cas par Etats, par groupes professionnels, et dans les collectivités restreintes est discutée par l'auteur. Un tableau permet de comparer les taux de morbidité des précédentes épidémies, dans des institutions, écoles, etc., avec ceux de 1957. Il y eut environ 4,5 millions de cas déclarés et 242 décès par million de cas. La mortalité a beaucoup varié d'un Etat à l'autre, ainsi que le montre un tableau qui fait ressortir aussi le contraste entre la gravité de la pandémie de 1918 et la bénignité de celle de 1957.

Parmi les signes cliniques, des nausées et vomissements, l'épistaxis et divers autres symptômes trahissaient l'effet pathogène du virus sur le foie. Outre des manifestations dysentériques, le virus a occasionné des troubles du système nerveux. On a signalé chez 21 enfants sur 420, hospitalisés pour grippe, des phénomènes cérébraux et méningés. La moitié d'entre eux moururent. La myocardite était évidente chez 16 de 123 cas soumis à un électrocardiogramme. Un virus A/Asia a été isolé du LCR d'une jeune fille atteinte de grippe et sujette à des crises d'épilepsie.

L'auteur décrit les caractères des virus isolés au cours de l'épidémie et mentionne les germes accompagnants, isolés de quelques cas mortels. Les examens sérologiques ont donné lieu à des constatations intéressantes, qui conduisent l'auteur à formuler des hypothèses sur la différence de constitution des virus actifs dans les poussées épidémiques restreintes et dans les pandémies. Le traitement du virus par l'éther a augmenté le pouvoir hémagglutinant de certaines souches pour les hématies d'oiseaux.

La vaccination n'a pu être appliquée en grand, car les premiers lots de vaccin n'ont été disponibles qu'à l'époque où la vague massive de l'épidémie diminuait déjà de violence.

La thérapeutique par l'iode (Lugol, Mandl) en badigeon de gorge, a été appliquée à certains groupes — avec témoins non traités — au début de la pandémie. Ce traitement a entraîné une chute brusque du nombre des nouveaux cas. L'usage de l'iode par voie intraveineuse a donné de bons résultats dans les cas graves, provoquant une baisse de température et la disparition de la toxémie.

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